Simultaneous Use of Hypertonic Saline and IV Furosemide for Fluid Overload: A Systematic Review and Meta-Analysis

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OBJECTIVES: To evaluate the efficacy of the simultaneous hypertonic saline solution and IV furosemide (HSS+Fx) for patients with fluid overload compared with IV furosemide alone (Fx).

DATA SOURCES: Electronic databases (MEDLINE, EMBASE, CENTRAL, Cochrane Database of Systematic Reviews, PsycINFO, Scopus, and WOS) were searched from inception to March 2020.

STUDY SELECTION: Randomized controlled trials on the use of HSS+Fx in adult patients with fluid overload versus Fx were included.

DATA EXTRACTION: Data were collected on all-cause mortality, hospital length of stay, heart failure–related readmission, along with inpatient weight loss, change of daily diuresis, serum creatinine, and 24-hour urine sodium excretion from prior to post intervention. Pooled analysis with random effects models yielded relative risk or mean difference with 95% CIs.

DATA SYNTHESIS: Eleven randomized controlled trials comprising 2,987 acute decompensated heart failure patients were included. Meta-analysis demonstrated that HSS+Fx was associated with lower all-cause mortality (relative risk, 0.55; 95% CI, 0.46–0.67; $p < 0.05$; $I^2 = 12\%$) and heart failure–related readmissions (relative risk, 0.50; 95% CI, 0.33–0.76; $p < 0.05$; $I^2 = 61\%$), shorter hospital length of stay (mean difference, −3.28 d; 95% CI, −4.14 to −2.43; $p < 0.05$; $I^2 = 93\%$), increased daily diuresis (mean difference, 583.87 mL; 95% CI, 504.92–662.81; $p < 0.05$; $I^2 = 76\%$), weight loss (mean difference, −1.76 kg; 95% CI, −2.52 to −1.00; $p < 0.05$; $I^2 = 57\%$), serum sodium change (mean difference, 6.89 mEq/L; 95% CI, 4.98–8.79; $p < 0.05$; $I^2 = 95\%$), and higher 24-hour urine sodium excretion (mean difference, 61.10 mEq; 95% CI, 51.47–70.73; $p < 0.05$; $I^2 = 95\%$), along with decreased serum creatinine (mean difference, −0.46 mg/dL; 95% CI, −0.51 to −0.41; $p < 0.05$; $I^2 = 89\%$) when compared with Fx. The Grading of Recommendation, Assessment, Development, and Evaluation certainty of evidence ranged from low to moderate.

CONCLUSIONS: Benefits of the HSS+Fx over Fx were observed across all examined outcomes in acute decompensated heart failure patients with fluid overload. There is at least moderate certainty that HSS+Fx is associated with a reduction in mortality in patients with acute decompensated heart failure. Factors associated with a successful HSS+Fx utilization are still unknown. Current evidence cannot be extrapolated to other than fluid overload states in acute decompensated heart failure.

KEY WORDS: fluid therapy; furosemide; heart failure; hypertonic saline solution; systematic review

Fluid management is of the utmost importance for the management of critically ill patients (1). Fluid overload (FO) prevalence in ICUs ranges from 15% to 50% (2, 3), and it is associated with multiple

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DOI: 10.1097/CCM.0000000000005174

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organ dysfunction and increased mortality (4–6). Loop diuretics are the cornerstone of therapy for FO; however, during critical illness, organ dysfunction, dysregulated interplay among organs, and alterations in the pharmacokinetics of diuretics can lead to an impaired diuretic response which is independently associated with worse clinical outcomes (7–11).

Several interventions have been proposed to overcome diuretic resistance (12, 13). In this regard, some studies in patients with acute decompensated heart failure (ADHF) had reported the simultaneous use of hypertonic saline solution (HSS) and IV furosemide (HSS+Fx) is more effective than loop diuretic alone (Fx) and had demonstrated improvement in both short- and long-term outcomes (14–26). The rationale for the use of HSS+Fx was initially attributed to its high osmotic property (16, 27, 28), but recent advances provide some new insights into the underlying mechanisms, including the correction of hyponatremia and hypochloremia, which are known to correlate with a high likelihood of diuretic resistance and mortality (29).

Two systematic reviews (SRs) (28, 30), compared the effect of HSS+Fx against Fx for patients with ADHF. Both showed HSS+Fx provided significant advantages on mortality, heart failure (HF)–related readmission, weight loss, hospital length of stay (LOS), and preservation of renal function.

After the publication of the two mentioned SRs, new studies have been published. The objective of this review was to determine the efficacy of HSS+Fx in the management of patients with FO compared with Fx, based on all the pertinent evidence.

METHODS

We conducted a SR of randomized clinical trials (RCTs) with meta-analysis following the recommendations by the Cochrane Handbook (31) and the Preferred Reporting Items for a SR and Meta-analysis statement (32). This SR was prospectively registered in the International Prospective Register of SRs (CRD42020173298).

Eligibility Criteria

Eligible studies had to be RCTs or observational studies that reported the use of HSS+Fx to increase diuretic efficiency in adults with FO requiring diuretic therapy. We excluded studies when their full-text was not available and studies evaluating HSS for other reasons than diuresis or did not have a comparison arm. We also excluded nonoriginal studies.

Search Strategy

The search strategy was designed and conducted by an experienced librarian with input from the study's principal investigators. A comprehensive search of several databases from each database's inception to March 17, 2020, was conducted. The databases included Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Ovid PsycINFO, Scopus, and Web of Science. The actual search strategy is available in the **supplemental data** (http://links.lww.com/CCM/G521). Reference lists of retrieved articles and review articles in the field were also searched to identify additional publications.

Study Selection

Two reviewers independently and in duplicate screened the abstracts for eligibility. Disagreements were upgraded to the next level of screening. Full texts of eligible abstracts were retrieved and screened in duplicate. Disagreements at this level were resolved by discussion and consensus. We calculated the inter-reviewer agreement beyond chance (κ) and recorded the reasons for exclusion during the full-text screening level.

Data Extraction

Data from eligible studies were independently extracted in duplicates into a prespecified web-based form, discrepancies were revisited by a third author. Extracted data included the following: publication details, study design details, patients demographics, details of intervention and control arms, definition, and assessments of the outcomes. When a study reported follow-up at different periods, outcomes with the longest follow-up were extracted.

Author Contact

The corresponding authors of the following RCTs (16, 18, 19, 21–23, 25) were contacted via E-mail to

evaluate the possibility of data duplication and missing data clarification.

Risk of Bias and Quality of Evidence Assessment

Using Version 2 of the Cochrane risk of bias tool for RCTs (33), two authors independently and in duplicate assessed the methodological quality of the included RCTs. The Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) approach (34) was followed to assess the certainty of the evidence for the outcomes. For each outcome, five domains (risk of bias, inconsistency, indirectness of evidence, imprecision of results, and publication bias) were evaluated. The overall certainty on the evidence was expressed in four categories (high, moderate, low, very low).

Statistical Analysis

The characteristics of the included studies and patients were summarized as descriptive statistics, continuous variables were summarized as mean (SD) or medians (interquartile range [IQR]), when appropriate. Categorical variables were summarized as counts (*n*) or percentages (%). As previously stated in our protocol, we were expecting moderate to substantial study level variability; therefore, data were pooled across studies using a random effects model to estimate treatment effects and reported as relative risk (RR) for dichotomous outcomes and mean difference (MD) for continuous outcomes with 95% CIs. Due to concerns of duplicated data, some RCTs (16, 18, 19, 21–23) were excluded in a sensitivity analysis due to the similarity of the sample size, demographics, and outcomes. To guarantee the representation of the cohort of patients from the RCTs mentioned above, we included the study with the largest sample size (23). Heterogeneity among included studies was explored by inspecting the forest plots and calculating I^2 statistic. Publication bias was assessed by funnel plots and Egger's test. Statistical analyses were performed using Review Manager Software 5 (Review Manager [RevMan] Version 5.3. The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and Stata (Version 16.0; StataCorp LLC, College Station, TX). A p value of less than 0.05 for effect sizes was considered to indicate statistical significance.

RESULTS

Search Results and Included Studies

The search identified 378 potentially relevant articles. Of which, 11 RCTs with 2,987 subjects were included and eligible for meta-analysis (16, 18, 19, 21–23, 25–27, 35, 36). All the screened observational studies did not meet the eligibility criteria. The process of identifying eligible trials is provided in **Figure S1** (http://links.lww.com/CCM/G522). The corresponding authors of the following seven RCTs (16, 18, 19, 21–23, 25) were contacted on two different separate occasions, without success. The kappa during the screening was substantial.

Characteristics of the Included Studies

All studies were conducted in ADHF patients with FO. General characteristics of the included studies are summarized in **Table 1**. Besides one multicenter RCT with a sample size of 1,927 patients (23), all other studies reported single-center data, and the majority of them with sample sizes smaller than 100 patients. Included studies enrolled patients with an average baseline serum creatinine (SCr) of 1.49 ± 0.22 mg/dL (SD). Furosemide was the most common loop diuretic used, and the dose ranged from 40 to 2,000 mg per day. Variable concentrations and amount of HSS were used, ranged from 1.4% to 7.5%, 150–500 mL per day, respectively. Five of 11 studies adjusted the concentration of HSS according to the individual's serum sodium level (16, 18, 21–23, 37), the other six RCTs used fixed concentrations of HSS in their investigations (19, 25–27, 35, 36). Nine RCTs provided the duration of intervention, ranged from 1 to 12 days (16, 19, 21, 22, 25–27, 35, 36). No major adverse effects of HSS+Fx were reported by these RCTs (**Table S1**, http://links.lww.com/CCM/G522).

Methodologic Quality and Risk of Bias

The overall risk of bias of RCTs was considered moderate to high (**Fig. 1**). Among the 11 included RCTs, six of them blinded participants and treating physicians (18, 19, 22, 26, 27, 36), three blinded only the participants (16, 21, 23) and two were open label (25, 35). The absence or poor concealment of the allocation sequence was considered as the leading cause of bias. One RCT was rated as a high risk for bias due to the

TABLE 1.
Description of Included Studies

References; Study Design	Enrollment Time	Inclusion Criteria	No. of Participants (% Female)	Mean Age, yr
Paterna et al (21); RCT	January 1996 to June 1998	Decompensated HF with EF < 35%, NYHA class IV, diuretic resistance, SCr < 2 mg/dL, and BUN ≤ 60 mg/dL	HSS+Fx 30 (36.67) Fx 30 (33.33)	HSS 73.57 Control 74.3
Licata et al (16); RCT	January 1996 to December 1999	Decompensated HF with EF < 35%, NYHA class IV, diuretic resistance, SCr < 2 mg/dL, and BUN ≤ 60 mg/dL	HSS+Fx 53 (37.74) Fx 54 (35.19)	HSS 74.7 Control 74.5
Paterna et al (22); RCT	January 2000 to January 2002	Decompensated HF with EF < 35%, NYHA class IV, diuretic resistance, SCr < 2 mg/dL, BUN ≤ 60 mg/dL, urinary volume < 500 mL/24 hr, and natriuresis < 60 mEq/24 hr	HSS+Fx 48 (37.5) Fx 46 (34.78)	HSS 74.7 Control 74.5
Parrinello et al (19); RCT	October 2007 to December 2008	Decompensated HF with EF < 40%, NYHA class IV, diuretic resistance, SCr < 2 mg/dL, BUN < 60 mg/dL, urinary volume < 500 mL/24 hr and natriuresis < 60 mEq/24 hr	HSS+Fx 66 (36.36) Fx 67 (34.33)	HSS 75.6 Control 76.3
Paterna et al (23); RCT	September 2000 to August 2007	Decompensated HF with EF < 40%, NYHA class III, diuretic resistance, SCr < 2.5 mg/dL, BUN < 60 mg/dL, and urinary volume < 800 mL/24 hr	HSS+Fx 953 (36.94) Fx 974 (37.17)	HSS 74.7 Control 73.4
Parrinello et al (18); RCT	NA	Decompensated HF with EF < 45%, NYHA class ≥ III, BNP > 100 pg/mL, SCr ≤ 2.5 mg/dL, and BUN ≤ 60 mg/dL	HSS+Fx 122 (40.98) Fx 126 (39.68)	HSS 74.9 Control 72
Issa et al (27); RCT	June 2008 to August 2010	Decompensated HF with EF ≤ 40%, SCr ≤ 3.0 mg/dL	HSS+Fx 20 (5) Fx 12 (41.67)	HSS 53.3 Control 41.5
Okuhara et al (35); RCT	July 2011 to January 2012	Decompensated HF with NYHA class ≥ III, SBP > 80 mm Hg, eGFR > 15 mL/min/1.73 m^2, and serum sodium < 148 mEq/L	HSS+Fx 22 (27.27) Fx 22 (36.36)	HSS 71 Control 73
Yayla et al (26); RCT	March 2011 to November 2012	Decompensated HF with pro-BNP > 300 pg/mL, SCr < 2.0 mg/dL, and SBP ≥ 90 mm Hg	HSS+Fx 14 (35.71) Fx 14 (50)	HSS 70.6 Control 71.7
Wan et al (25); RCT	January 2010 to January 2011	Decompensated HF with EF < 40%, NYHA class III, diuretic resistance; SCr < 1.73 mg/dL, BUN < 60 mg/dL, and urinary volume < 500 mL/24 hr.	HSS+Fx 132 (59.85) Fx 132 (57.58)	HSS 60.62 Control 61.18
Engelmeier et al (36); RCT	November 2009 to 2011	Decompensated HF with eGFR < 60 mL/min	HSS+Fx 25 (NA) Fx 25 (NA)	79.6

BNP = B-type natriuretic peptide, BUN = blood urea nitrogen, EF = ejection fraction, eGFR = estimated glomerular filtration rate, Fx = IV furosemide, HF = heart failure, HSS = hypertonic saline solution, NA = not available, NYHA = the New York Heart Association functional classification, QD = once daily, RCT = randomized controlled trial, SBP = systolic blood pressure, SCr = serum creatinine.

Baseline Serum Creatinine in mg/dL (SD)	Interventions	Control	Duration and Follow-Up Time
1.6 (0.05) 1.65 (0.07)	IV 30-min infusion of 150 mL of 1.4–4.6% NaCl plus furosemide 500–1,000 mg bid	IV furosemide 500–1,000 mg bid	Duration: 6–12 d Follow-up: 6–12 mo
1.60 (0.05) 1.65 (0.05)	IV 30-min infusion of 150 mL of 1.4–4.6% NaCl plus furosemide 500–1,000 mg bid	IV furosemide 500–1,000 mg bid	Duration: 6–12 d Follow-up: 31 ± 14 mo
1.51 (0.05) 1.55 (0.05)	IV 30-min infusion of 150 mL of 1.4–4.6% NaCl plus furosemide 500–1,000 mg bid	IV furosemide 500–1,000 mg bid	Duration: 4–6 d Follow-up: 30 d
1.50 (0.3) 1.4 (0.5)	IV 20-min infusion of 150 mL of 3.0% NaCl plus furosemide 250 mg bid	IV 20-min infusion of 150 mL of 0.9% NaCl plus furosemide 250 mg bid	Duration: 6 d Follow-up: NA
1.65 (0.05) 1.61 (0.05)	IV 30-min infusion of 150 mL of 1.4–4.6% NaCl plus furosemide 250 mg bid	IV furosemide 250 mg bid	Duration: NA Follow-up: 57 ± 15 mo
1.22 (0.4) 1.18 (0.6)	IV 30-min infusion of 150 mL of 1.4–4.6% NaCl plus furosemide 250 mg bid	IV furosemide 250 mg bid	Duration: NA Follow-up: NA
1.72 (0.47) 1.58 (0.48)	IV 1 hr infusion of 100 mL of 7.5% NaCl plus furosemide bid	IV 1 hr infusion of 100 mL of 0.9% NaCl plus furosemide bid	Duration: 3 d Follow-up: 69.5 d (32.2–164.7 d)
1.56 (0.85) 1.45 (0.77)	IV 24 hr infusion of 500 mL of 1.7% NaCl plus furosemide 40 mg QD	IV 24 hr infusion of 500 mL of 5% glucose plus furosemide 40 mg QD	Duration: 24 hr Follow-up: NA
0.96 (0.29) 0.93 (0.32)	IV 30-min infusion of 150 mL of 1.95% NaCl plus furosemide 160 mg QD	IV furosemide 80 mg bid	Duration: 48 hr Follow-up: NA
NA	IV 1 hr infusion of 100 mL of compound hypertonic saline solution (2.8% NaCl with 0.2% KCl and 0.9% $MgSO_4$) plus furosemide 100 mg bid	IV furosemide 100 mg bid	Duration: 48 hr Follow-up: 4 yr
1.78 (0.62) 1.79 (0.49)	IV 30-min infusion of 150 mL of 2.4% NaCl plus furosemide 250 mg	IV 30-min infusion of 150 mL of 0.9% NaCl plus furosemide 80 mg	Duration: 4 and 5 doses in HSS and control group, respectively. Follow-up: NA

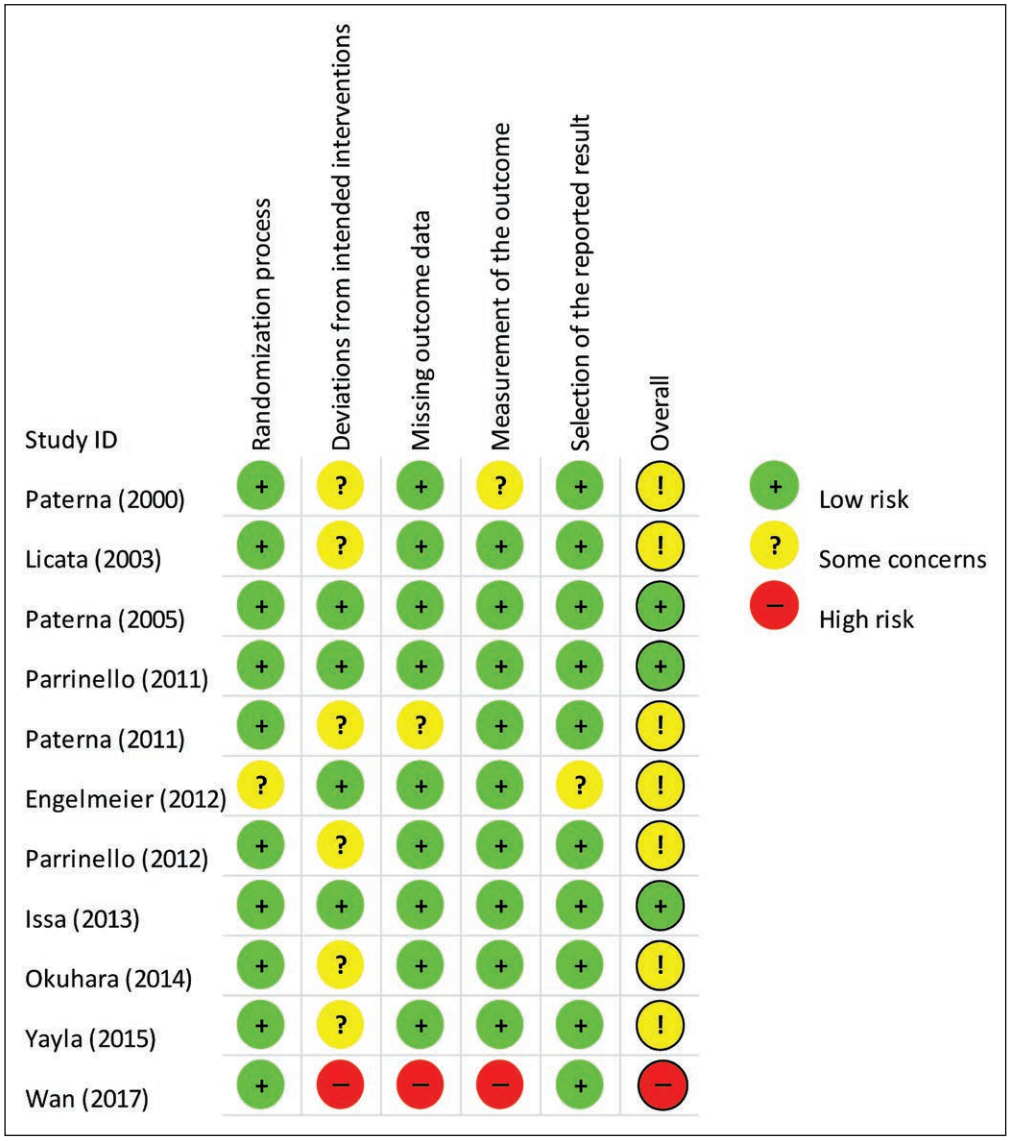

Figure 1. Summary of the risk of bias assessments for the 11 randomized controlled trials included in the systematic review.

absence of blinding and a high rate of loss to follow-up (11.36%) (25).

Publication Bias Assessment

We could not identify publication bias statistically based on the symmetry of funnel plots and the results of Egger's test for all-cause mortality ($p = 0.80$), hospital LOS ($p = 0.87$), daily diuresis ($p = 0.64$), and change of serum sodium ($p = 0.39$); the funnel plots are presented in **Figures S2–S5** (http://links.lww.com/CCM/G522). There was some concern for publication bias (funnel asymmetry and significant Egger's test) for the outcomes of HF-related readmission ($p < 0.05$), weight loss ($p < 0.05$), change of SCr ($p < 0.05$), and 24-hour urine sodium excretion ($p < 0.05$); the funnel plots are presented in **Figures S6–S9** (http://links.lww.com/CCM/G522). However, publication bias assessment was not used to down rate the certainty of the evidence as the number of studies in these analyses was small making these tests not reliable enough. These findings could be chance findings due to multiple testing.

Meta-Analysis

The GRADE evidence profile is presented in **Table 2**.

All-Cause Mortality. It was assessed in six RCTs with 2,298 patients (16, 21–23, 25, 27). Patients treated with HSS+Fx had a reduced risk of all-cause mortality (6 RCTs; RR 0.55; 95% CI, 0.46–0.67; $p < 0.05$; $I^2 = 12\%$) (**Fig. 2**), compared with Fx. The follow-up period varied from 1 to 57 months. The heterogeneity was considered low after the visual analysis of the forest plot and considering the value of the I^2. Owing to concerns related to the duplication of the data in some included RCTs (16, 21–23), we performed the sensitivity analysis previously explained in methods. The analysis continued to show a reduced risk of all-cause mortality (3 RCTs; RR, 0.63; 95% CI, 0.41–0.95; $p < 0.05$; $I^2 = 57\%$) in HSS+Fx compared with Fx (**Fig. S10**, http://links.lww.com/CCM/G522), similar to the one including all the trials reporting all-cause mortality. The GRADE overall certainty of the evidence was moderate due to the risk of bias.

HF-Related Readmission. It was assessed in four RCTs with 2,032 patients (16, 21–23), the average

follow-up time varied from 1 (22) to 57 months (23). Compared with Fx, treatment with HSS+Fx was associated with a reduced risk of HF-related readmission (4 RCTs; RR, 0.50; 95% CI, 0.33–0.76; $p < 0.05$; $I^2 = 61\%$) (**Fig. 3**). After visual inspection of the forest plot, the calculated heterogeneity by the I^2 statistics was deemed unimportant. The sensitivity analysis explained above demonstrated a similar result (1 RCT; RR, 0.54; 95% CI, 0.46–0.64; $p < 0.05$; I^2 not applicable) (**Fig. S11**, http://links.lww.com/CCM/G522). The GRADE overall certainty of the evidence was moderate due to the risk of bias.

Hospital LOS. It was assessed in nine RCTs with 2,911 patients (16, 18, 19, 21–23, 25, 26, 36). Hospital LOS was 3 days shorter in patients treated with HSS+Fx compared with Fx (9 RCTs; MD, –3.28 d; 95% CI, –4.14 to –2.43; $p < 0.05$; $I^2 = 93\%$) (**Fig. S12**, http://links.lww.com/CCM/G522). After visual inspection of the forest plot, the substantial heterogeneity was deemed unimportant. Sensitivity analysis explained above indicated that the difference of LOS remains statistically significant (4 RCTs; MD, –2.37 d; 95% CI, –3.31 to –1.44; $p < 0.05$; $I^2 = 87\%$) (**Fig. S13**, http://links.lww.com/CCM/G522). The GRADE overall certainty of the evidence was moderate due to the risk of bias.

Daily Diuresis. It was assessed in seven RCTs with 2,833 patients (16, 18, 19, 21–23, 25). The HSS+Fx significantly increased daily diuresis compared with Fx (7 RCTs; MD, 583.87 mL; 95% CI, 504.92–662.81; $p < 0.05$; $I^2 = 76\%$) (**Fig. S14**, http://links.lww.com/CCM/G522). The substantial heterogeneity found in the analysis was deemed unimportant. Sensitivity analysis explained above still showed a significant increase of daily diuresis (2 RCTs; MD, 531.35 mL; 95% CI, 497.19–565.50; $p < 0.05$; $I^2 = 0\%$) (**Fig. S15**, http://links.lww.com/CCM/G522). The GRADE overall certainty of the evidence was moderate due to the risk of bias.

Weight Loss. It was assessed in 10 RCTs with 2,723 patients (16, 18, 19, 21–23, 26, 27, 35, 36). Greater weight loss was achieved after HSS+Fx (10 RCTs; MD, –1.76 kg; 95% CI, –2.52 to –1.00; $p < 0.05$; $I^2 = 57\%$) when compared with Fx (**Fig. S16**, http://links.lww.com/CCM/G522). The moderate heterogeneity found in the analysis was deemed unimportant. Sensitivity analysis explained above still indicated a significant greater weight loss (5 RCTs; MD, –0.90 kg; 95% CI, –1.30 to –0.50; $p < 0.05$; $I^2 = 0\%$) (**Fig. S17**, http://links.lww.com/CCM/G522). The GRADE overall certainty of the evidence was moderate due to the risk of bias.

Change in SCr. It was assessed in 10 RCTs with 2,723 patients (16, 18, 19, 21–23, 26, 27, 35, 36). Compared with Fx, treatment with HSS+Fx was associated with a greater decrease of SCr (10 RCTs; MD, –0.46 mg/dL; 95% CI, –0.51 to –0.41; $p < 0.05$; $I^2 = 89\%$) (**Fig. S18**, http://links.lww.com/CCM/G522). A loss of statistical difference was observed in sensitivity analysis explained above (5 RCTs; MD, –0.11 mg/dL; 95% CI, –0.48 to 0.26; $p = 0.57$; $I^2 = 92\%$) (**Fig. S19**, http://links.lww.com/CCM/G522). The heterogeneity was deemed to be important. The GRADE overall certainty of the evidence was low due to the risk of bias, heterogeneity, and potential data duplication.

Change in Serum Sodium. It was assessed in 10 RCTs with 2,937 patients (16, 18, 19, 21–23, 25–27, 35). Expectedly, compared with Fx, a greater increase of serum sodium was observed in patients treated with HSS+Fx (10 RCTs; MD, 6.89 mEq/L; 95% CI, 4.98–8.79; $p < 0.05$; $I^2 = 95\%$) (**Fig. S20**, http://links.lww.com/CCM/G522). The heterogeneity of data was deemed negligible. Sensitivity analysis explained above still indicated a significant greater increase of serum sodium (5 RCTs; MD, 3.73 mEq/L; 95% CI, 0.60–6.85; $p < 0.05$; $I^2 = 97\%$) (**Fig. S21**, http://links.lww.com/CCM/G522). The GRADE overall certainty of the evidence was moderate due to the risk of bias.

Change in 24-Hour Urine Sodium Excretion. It was assessed in five RCTs with 2,321 patients (16, 19, 21–23). HSS+Fx was associated with a greater increase of 24-hour urine sodium excretion when compared with Fx (5 RCTs; MD, 61.10 mEq; 95% CI, 51.47–70.73; $p < 0.05$; $I^2 = 95\%$) (**Fig. S22**, http://links.lww.com/CCM/G522). The heterogeneity was deemed to be unimportant. The sensitivity analysis demonstrated a similar result (1 RCT; MD, 48.40 mEq; 95% CI, 47.48–49.32; $p < 0.05$; I^2 not applicable) (**Fig. S23**, http://links.lww.com/CCM/G522). The GRADE overall certainty of the evidence was moderate due to the risk of bias.

DISCUSSION

In this SR with meta-analyses involving adult patients with ADHF, we observed that HSS+Fx was associated with increased daily diuresis, weight loss, serum sodium change, and urine sodium excretion, as well as a reduction in SCr, hospital LOS, HF-related

TABLE 2.
The Evidence Profile According to the Grading of Recommendations Assessment, Development, and Evaluation Approach

Certainty Assessment						
No. of Studies	**Study Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Considerations**
All-cause mortality (follow-up: range 1–57 mo)						
6	Randomized trials	Serious[a]	Not serious	Not serious	Not serious	None
Heart failure-related readmission (follow-up: range 1–57 mo)						
4	Randomized trials	Serious[c]	Not serious	Not serious	Not serious	Concern for publication bias [d]
Length of hospital stay						
9	Randomized trials	Serious[a]	Not serious	Not serious	Not serious	None
Change of daily diuresis from prior to post intervention						
7	Randomized trials	Serious[a]	Not serious	Not serious	Not serious	None
Weight loss from prior to post intervention						
10	Randomized trials	Serious[c]	Not serious	Not serious	Not serious	Concern for publication bias[d]
Change of serum creatinine from prior to post intervention						
10	Randomized trials	Serious[c]	Very serious[e]	Not serious	Not serious	Concern for publication bias[d]
Change of 24 hr urine sodium excretion from prior to post intervention						
5	Randomized trials	Serious[c]	Not serious	Not serious	Not serious	Concern for publication bias[d]

RR = risk ratio, MD = mean difference, NA = not applicable.

[a]The overall risk of bias was adjudicated as moderate to high.

[b]The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[c]The overall risk of bias was adjudicated as moderate.

[d]Publication bias detected by inspection of funnel plot and Egger's test.

[e]The effect direction was inconsistent, and the estimate was not robust to potential data duplication.

Question: hypertonic saline plus furosemide compared with furosemide alone in adult acute decompensated heart failure patients

Grading of Recommendation, Assessment, Development, and Evaluation Working Group grades of evidence. High certainty (⨁⨁⨁⨁): we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty (⨁⨁⨁◯): we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty (⨁⨁◯◯): our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty (⨁◯◯◯): we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

No. of Patients		Effect			
Hypertonic Saline Plus Furosemide	Furosemide Alone	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
174/1,153 (15.1%)	313/1,145 (27.3%)	**RR, 0.55** (0.46–0.67)	**123 fewer per 1,000** (from 148 fewer to 90 fewer)[b]	⨁⨁⨁◯ Moderate	Critical
188/1,012 (18.6%)	372/1,020 (36.5%)	**RR, 0.50** (0.33–0.76)	**182 fewer per 1,000** (from 244 fewer to 88 fewer)[b]	⨁⨁⨁◯ Moderate	Critical
1,443	1,468	NA	MD, **3.28 d fewer** (4.14 fewer to 2.43 fewer)	⨁⨁⨁◯ Moderate	Important
1,404	1,429	NA	MD, **583.87 mL more** (504.92 more to 662.81 more)	⨁⨁⨁◯ Moderate	Important
1,353	1,370	NA	MD, **1.76 kg lower** (2.52 lower to 1 lower)	⨁⨁⨁◯ Moderate	Important
1,353	1,370	NA	MD, **0.46 mg/dL lower** (0.51 lower to 0.41 lower)	⨁⨁◯◯ Low	Not important
1,150	1,171	NA	MD, **61.1 mEq/24 hr higher** (51.47 higher to 70.73 higher)	⨁⨁⨁◯ Moderate	Not important

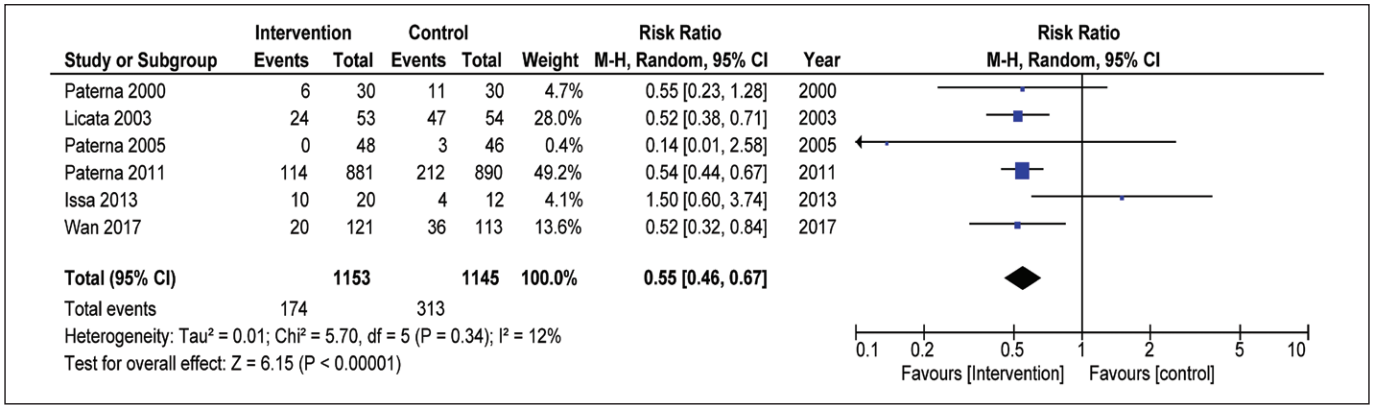

Figure 2. The forest plot for the comparison of the risk of all-cause mortality. df = degrees of freedom, M-H = Mantel-Haenszel method.

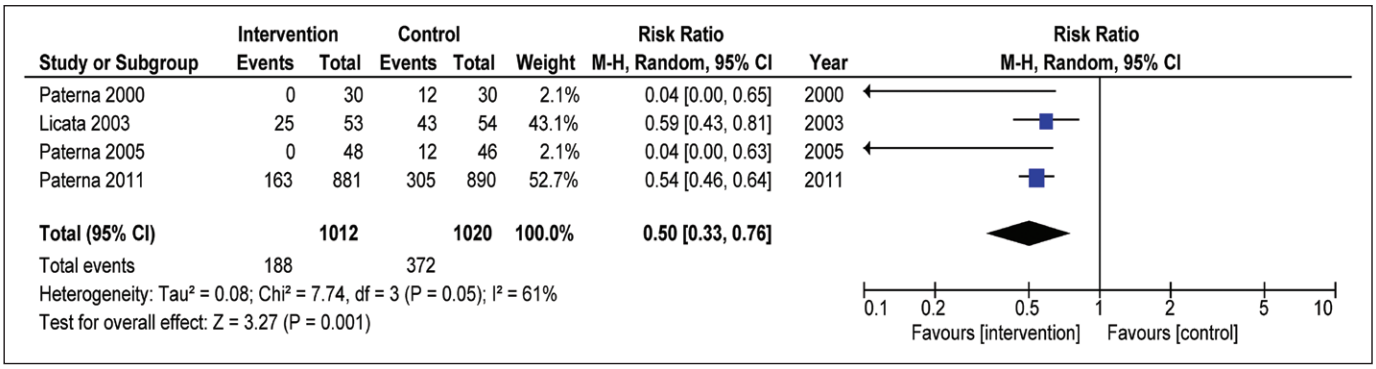
Intervention
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
Paterna 2000 0 30 12 30 2.1% 0.04 [0.00, 0.65] 2000
Licata 2003 25 53 43 54 43.1% 0.59 [0.43, 0.81] 2003
Paterna 2005 0 48 12 46 2.1% 0.04 [0.00, 0.63] 2005
Paterna 2011 163 881 305 890 52.7% 0.54 [0.46, 0.64] 2011
Total (95% CI) 1012 1020 100.0% 0.50 [0.33, 0.76]
Total events 188 372
Heterogeneity: Tau² = 0.08; Chi² = 7.74, df = 3 (P = 0.05); I² = 61%
Test for overall effect: Z = 3.27 (P = 0.001)
0.1 0.2 0.5 1 2 5 10
Favours [intervention] Favours [control]

Figure 3. The forest plot for the comparison of the risk of heart failure–related readmission. df = degrees of freedom, M-H = Mantel-Haenszel method.

readmission, and all-cause mortality. The GRADE certainty of the evidence ranged from low to moderate.

The most surprising finding was that the all-cause mortality benefit of 123 fewer deaths per 1,000 patients was beyond the associated effect on daily diuresis and weight loss, suggesting that the benefits of HSS+Fx were not just related to its diuretic properties. It is known that loop diuretics block the tubuloglomerular feedback (38); therefore, providing a sodium load could decrease the adrenergic and renin-angiotensin systems activation and their associated detrimental effects on the cardiovascular system, improving outcome beyond the associated diuresis.

With the advantages of availability, noninvasive nature, and cost-effectiveness of HSS+Fx, the outlook of such an approach as an advanced therapy for the management of ADHF seems promising. However, the low quality of the evidence restricts the certainty of this approach. Although the long-standing concept that patients with HF benefit from aggressive sodium restriction has been questioned by recent RCTs (39, 40), the lack of a true mechanistic explanation of the benefit of HSS+Fx makes its implementation challenging. Rapid correction of hyponatremia (> 8 mEq/L at 24 hr) in patients with serum sodium < 120 mEq/L is associated with the risk of osmotic demyelination (41). Our analysis indicated that the median baseline serum sodium was 136.8 mEq/L (IQR, 135.7–138.1 mEq/L), and the mean increase of serum sodium after the intervention was 3.48 mEq/L (SD 3.21) in patients treated with HSS+Fx (16, 18, 19, 21–23, 25–27, 35). Even though HSS+Fx was reported to be safe in included RCTs, the use of this treatment in hyponatremic patients should be considered with caution. Also, the majority of RCTs enrolled patients with ejection fraction less than 40% and at risk of moderate to severe kidney impairment (SCr ≤ 3.0 mg/dL). Thus, the effect and safety of HSS+Fx in ADHF patients with preserved ejection fraction or severe kidney dysfunction were unclear. Additionally, the optimal dose, duration, and concentration combination of this approach remain undetermined. Therefore, future research should include the fundamental investigation of mechanisms, and more high-quality studies are needed to find the

right doses and duration of this intervention, as well as indications and factors related to the success of this intervention.

Two previous SRs analyzed five outcomes in nine and 10 RCTs. Both demonstrated that HSS+Fx impacted each examined outcome in ADHF patients with FO favorably compared with Fx (28, 30). Most of their findings were echoed in our SR except for the change of SCr. We demonstrated that current evidence could not adequately support the kidney protective role of HSS+Fx in ADHF. Besides, some limitations of the previous SRs may have negatively impacted the reliability of their findings. First, the quality of evidence assessment was absent in both SRs. Second, both SRs included one ineligible RCT, which 0.9% saline load (15 mL/kg) after 8-day treatment of ADHF patients as the primary intervention (24). This RCT deviated from routine clinical practices and the intended intervention of the SRs. Finally, both SRs included six RCTs from the same center (16, 18, 19, 21–23) with likely duplicated data. These SRs failed to address this important methodological limitation. We updated previous findings in line with the rigorous methodological standards and examined potential data duplication via sensitivity analyses. These approaches increase the certainty of our findings.

Our SR has several strengths, including the most up-to-date summary of the evidence, comprehensive assessment of clinically meaningful outcomes, the examination of potential data duplication, and assessment of the quality of evidence. Also, furosemide is the most commonly evaluated and clinically used loop diuretic. Therefore, using furosemide in our study likely provides generalizable information. We performed an extensive search with dates going from 1966 to 2020, so all the available potential body of evidence was evaluated for inclusion. This allowed us to recognize the timeline for the use of HSS+Fx in patients with FO (i.e., RCTs from 2000 [21] to 2017 [25] and the latest observational data in March 2020 [14]).

Also, our study has several limitations. It is evident that the largest RCT (23) is the one with the biggest weight on our meta-analyses and is likely driving the results. Fortunately, we were able to perform a meta-analysis in all our predefined outcomes, three of them being patient-centered outcomes with considerable clinical significance, and we evaluate the heterogeneity in each of them, showing that other smaller RCTs reproduced similar estimates. Another limitation is that due to the small number of included studies, publication bias assessment was not reliable. However, the estimates of all-cause mortality, hospital LOS, daily diuresis, and serum sodium change appear not to be affected by this type of bias. The majority of the included patients had ADHF with reduced ejection fraction and moderate to severe kidney impairment. These patients have historically considered being very sensitive to sodium loading. Our SR found no adverse effect when compared with controls. Therefore, we assume that cautious extrapolation to patients with preserved ejection fraction and normal kidney function would be potentially safe. The generalizability of the reported effectiveness outcomes would be challenging to extrapolate to other populations. The synergistic effect of HSS and furosemide cannot be extrapolated to other states of FO. Nevertheless, we believe that the effects of HSS+Fx in decreasing diuretic resistance are independent of the etiology of the FO state, and it is reasonable to expect a similar result in patients with other FO states.

CONCLUSIONS

Current evidence suggests that HSS+Fx is a promising alternative therapy in the treatment of ADHF, particularly those with reduced ejection fraction and moderate to severe kidney impairment, with the potential possibility to improve patient-centered outcomes such as mortality, LOS, and readmission rate. The lack of RCTs in other FO states limits the generalizability of our findings. The focus needs to be placed on designing trials to identify the right doses and length of therapy of HSS+Fx for patients with ADHF as well designing RCTs including patients with other FO states.

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Drs. Kashani, Gajic, and Domecq contributed to concept and design. Dr. Prokop contributed to search strategy. Drs. Liu and Domecq contributed to abstract review. Drs. Liu, Gao, and Domecq contributed to full-text review. Drs. Liu, Gao, and Domecq contributed to data extraction. Drs. Liu, Peng, Gao, and Domecq contributed to quality assessment. Drs. Liu, Peng, and Domecq contributed to data analysis and drafting of the article. Drs. Prokop, Kashani, Dong, and Murad contributed to critical revision of the article. All the authors approved the final draft. Drs. Liu and Domecq had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Data will be provided under request to the corresponding author.

The authors have disclosed that they do not have any potential conflicts of interest.

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